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(54) Title: USE OF INHIBITORS OF CYCLOOXYGENASE IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

(57) Abstract

The invention describes a method of treating neurodegenerative disorders such as Alzheimer's Disease by using a COX-2 inhibitor.

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USE OF INHIBITORS OF CYCLOOXYGENESE IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

The present invention relates to a method of treating Alzheimers disease and to the use of compounds in the preparation of a medicament for the treatment of Alzheimers disease.

US Patent No. 5,192, 753 states inter alia that dementia in human beings may be treated with compounds selected from the non-steroidal anti-inflammatory group of cyclooxygenase inhibitors. The non-steroid anti-inflammatory drugs (NSAIDs) referred to in US Patent No. 5,192,753 are all agents which possess significant ability to inhibit cyclooxygenase type 1 (COX-1). A number of publications have also occurred in the scientific literature which disclose that agents such as acetylacetic acid and indomethecin, which are generally viewed as potent inhibitors of COX-1, can be used in the treatment of Alzheimers disease; see for example:

McGeer et al, Lancet, 1990:335, 1037;

Rogers et al, Neurology, 1993:43; 1609-1611;

McGeer et al, Neurology, 1992:42, 447-449; and

Breitner et al, Neurology, 1994, 227-232.

Cyclooxygenase (COX) exists in the human as cyclooxygenase type I (COX-I) and cyclooxygenase type II (COX-II). Hitherto there has been no suggestion that COX-II plays any role in Alzheimers disease. Indeed there has been no evidence which demonstrates that COX-II plays a part in any human central nervous system disorder. COX-II is inducilible by a number of agents such as mitogen, endotoxin, cytokines and the like but none of these agents which have been demonstrated as inducing COX-II have been shown to be causitive in Alzheimers disease.

However, it has now been unexpectedly discovered that COX-II is found in neurones in the temporal lobes of humans suffering from Alzheimers disease.

The present invention provides a method of treating a neurodegenerative disease and in particular Alzheimers disease which comprises administering to a human in need thereof a therapeutically effective amount of a non-steroid COX-II inhibitor.

From antoher aspect this invention provides the use of a COX-II inhibitor in the manufacture of a medicament for the treatment of a neurodegenerative disease and in particular Alzheimers disease.

When used herein the term "treating" includes treatment of existing disease and prophylactic treatment of those at risk of developing the disease.

When used herein the term "COX-II" inhibitor means a compound able to inhibit human COX-II enzyme without causing relatively significant inhibition of human COX-I enzyme. Generally compounds which bind at least 10 times as well to COX-I receptors as to COX-II receptors (ie will have a IC_{50} COX-II receptor only one thenth the neumerical value of the COX-I receptor) are chosen for use in the invention, more aptly 20 times as well, favourably 50 times as well most favourably at least 100 times as well, and preferably at least 1000 times as well

The COX-II inhibitors for use in this invention are most aptly those which are highly brain penetrant so that the maximum concentration of COX-II inhibitor after administration of the anti-neurodegenerative for example the anti-alzheimer effective dose of COX-II inhibitor is at least the binding IC_{50} value and preferably at least 10 times that value for example at least 100 times the binding IC_{50} value.

The COX-II inhibitor may be of any structural type other than a steroid. However, most aptly the COX-II inhibitor employed in this invention is not a carboxylic acid or a salt thereof. Most favourably it will possess a SO_2CH_3, $NHSO_2CH_3$, SO_2NH_2, SO_2NHCH_3 or like substituent on an aromatic ring especially on a phenyl ring.

Our investigations and statements made in the more recent of the following patents indicate that Cox-II inhibitors may be found in US Patents Nos 4,375,479; 4,590,205; 4,820,827; 5,343,991; EP 0418845; WO 91/19708; WO 94/15932 and WO 94/13635. Each of the above documents is incorporated herein by cross reference.

Thus in one aspect this invention provides a method of treating a neurodegenerative disease and in particular Alzheimers disease which comprises administering to a patient therapeutically effective amount of a compound generically disclosed (and preferably a compound specifically described) in US Patent No 4,375,479; 4,590,205; 4,820,827; 5,344,991; EP 0418845; WO 91/19708; WO 94/15932 or WO 94/13635.

The invention also provides the use of such compounds in the manufacture of a medicament for the treatment of neurodegenerative disease and in particular Alzheimers disease.

Favourably the COX-II inhibitor employed is one described in WO/94 26751 (published November 24, 1994); WO 94/20480 (published September 15, 1994), US 5,436,265 (issued July 25, 1995), WO 95/00501 (published January 5, 1995); WO 95/18799 (published July 13, 1995) and GB 2283745 (published May 17, 1995) all of which are included herein by cross-reference (ie may be read together with this Specification).

Most favourably the COX-II inhibitor employed is one described in WO 95/00501, especially these wherein R^1 is a SO_2CH_3 group.

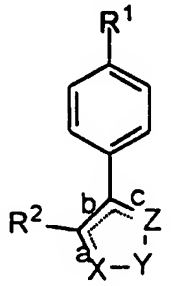
Preferred compounds for use in this invention are compounds named in WO 95/00501.

The medicaments for treating neurodegenerative disease may be formulated as described in the aforementioned referenced documents. The medicament may be employed in the doses and regimens set out in the aforementioned referenced documents with respect to the treatment of diseases which benefit from the administration of a COX-II inhibitor.

It is a great advantage of this invention that treatment may be carried out without causing gastric side effects of the type that can occur

when COX I inhibitors are used for prolonged periods. Since neurodegenerative diseases such as Alzheimers disease are generally progressive treatment may need to take place for a number of years. Thus the provision of medicaments which are surprisingly effective without any significant tendency to cause gastric side effects at the therapeutic dose is of great use particularly to the elderly. The use of medicaments of this invention for the treatment of patients who are assymptomatic is also envisaged especially in those cases where genetic information suggests that the patient is likely to develop Alzheimers disease or other neurodegenerative disease especially those which may be termed dementia, for example senile demintia or pre-senile dementia.

The invention encompasses the use of a novel compound of Formula I useful in the treatment of a neurodegenerative disease such as Alzheimers Disease:



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or pharmaceutically acceptable salts thereof wherein:
X–Y–Z–is selected from the group consisting of:

(a) -$CH_2CH_2CH_2$-,
(b) -$C(O)CH_2CH_2$-,
(c) -$CH_2CH_2C(O)$-,
(d) -$CR^5(R^{5'})$-O-C(O)-,
(e) -C(O)-O-$CR^5(R^{5'})$-,
(f) -CH_2-NR^3-CH_2-,
(g) -$CR^5(R^{5'})$-NR^3-C(O)-,
(h) -CR^4=$CR^{4'}$-S-,
(i) -S-CR^4=$CR^{4'}$-,

(j) -S-N=CH-,
(k) -CH=N-S-,
(l) -N=CR^4-O-,
(m) -O-CR4=N-
(n) -N=CR^4-NH-;
(o) -N=CR^4-S-, and
(p) -S-CR^4=N-;
(q) -C(O)-NR^3-CR^5(R$^{5'}$)-;
(r) -R^{3}N-CH=CH- provided R^{1}is not -S(O)$_2$Me
(s) -CH=CH-NR^3- provided R^{1}is not -S(O)$_2$Me

when side b is a double bond, and sides a an c are single bonds; and

X–Y–Z–is selected from the group consisting of:
(a) =CH-O-CH=, and
(b) =CH-NR^3-CH=,
(c) =N-S-CH=,
(d) =CH-S-N=,
(e) =N-O-CH=,
(f) =CH-O-N=,
(g) =N-S-N=,
(h) =N-O-N=,

when sides a and c are double bonds and side b is a single bond;
R^1 is selected from the group consisting of
(a) S(O)$_2$CH$_3$,
(b) S(O)$_2$NH$_2$,
(c) S(O)$_2$NHC(O)CF$_3$,
(d) S(O)(NH)CH$_3$,
(e) S(O)(NH)NH$_2$,
(f) S(O)(NH)NHC(O)CF$_3$,
(g) P(O)(CH$_3$)OH, and
(h) P(O)(CH$_3$)NH$_2$,

R^2 is selected from the group consisting of
(a) C$_{1-6}$alkyl,
(b) C$_3$, C$_4$, C$_5$, C$_6$, and C$_7$, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of

(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,
(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^5)(R^6)-OH$,
(12) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^5$;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or
the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of

(1) hydrogen,
(2) halo, including fluoro, chloro, bromo and iodo,
(3) C_{1-6}alkyl,
(4) C_{1-6}alkoxy,
(5) C_{1-6}alkylthio,
(6) CN,
(7) CF_3,
(8) N_3,
(9) $-C(R^5)(R^6)-OH$, and
(10) $-C(R^5)(R^6)-O-C_{1-4}$alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^3 is selected from the group consisting of

(a) hydrogen,
(b) CF_3,
(c) CN,

(d) C_{1-6}alkyl,
(e) hydroxyC_{1-6}alkyl,
(f) -C(O)-C_{1-6}alkyl,
(g) optionally substituted
(1) -C_{1-5} alkyl-Q,
(2) -C_{1-3}alkyl-O-C_{1-3}alkyl-Q,
(3) -C_{1-3}alkyl-S-C_{1-3}alkyl-Q,
(4) -C_{1-5} alkyl-O-Q, or
(5) -C_{1-5} alkyl-S-Q,
wherein the substituent resides on the alkyl and the substituent is C_{1-3}alkyl;
(h) -Q

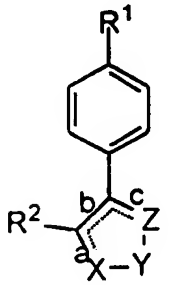
R^4 and $R^{4'}$ are each independently selected from the group consisting of
(a) hydrogen,
(b) CF_3,
(c) CN,
(d) C_{1-6}alkyl,
(e) -Q,
(f) -O-Q;
(g) -S-Q, and
(h) optionally substituted
(1) -C_{1-5} alkyl-Q,
(2) -O-C_{1-5} alkyl-Q,
(3) -S-C_{1-5} alkyl-Q,
(4) -C_{1-3}alkyl-O-C_{1-3}alkyl-Q,
(5) -C_{1-3}alkyl-S-C_{1-3}alkyl-Q,
(6) -C_{1-5} alkyl-O-Q,
(7) -C_{1-5} alkyl-S-Q,
wherein the substituent resides on the alkyl and the substituent is C_{1-3}alkyl, and

R^5, $R^{5'}$, R^6, R^7 and R^8 are each independently selected from the group consisting of
(a) hydrogen,
(b) C_{1-6}alkyl,
or R^5 and R^6 or R^7 and R^8 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q is CO_2H, CO_2-C_{1-4}alkyl, tetrazolyl-5-yl, $C(R^7)(R^8)(OH)$, or $C(R^7)(R^8)(O$-C_{1-4}alkyl);

provided that when X-Y-Z is -S-CR^4= $CR^{4'}$, then R^4 and $R^{4'}$ are other than CF_3 .

One Class within this embodiment are the compounds of formula I



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or pharmacetically acceptable salts thereof wherein:
X-Y-Z- is selected from the group consisting of -C(O)-O-$CR^5(R^{5'})$- when side b is a double bond, and sides a and c are single bonds; and
R^1 is selected from the group consisting of

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,

R^2 is selected from the group consisting of

(a) C_{1-6}alkyl,
(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,
(c) heteroaryl
(d) benzoheteroaryl
(e) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of
(1) hydrogen,
(2) halo,
(3) C_{1-6}alkoxy,
(4) C_{1-6}alkylthio,
(5) CN,
(6) CF_3,
(7) C_{1-6}alkyl,
(8) N_3,

(9) $-CO_2H$,
(10) $-CO_2-C_{1-4}$alkyl,
(11) $-C(R^5)(R^6)-OH$,
(12) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(13) $-C_{1-6}$alkyl$-CO_2-R^5$;

R^5, $R^{5'}$ and R^6 are each independently selected from the group consisting of

(a) hydrogen,
(b) C_{1-6}alkyl,

or R^5 and R^6 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

For purposes of this specification alkyl is defined to include linear, branched, and cyclic structures, with C_{1-6}alkyl including including methyl, ethyl, propyl, 2-propyl, s- and t-butyl, butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C_{1-6}alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C_{1-6}alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

Heteroaryl includes furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,3-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, and the like.

Benzoheteroaryl includes the above heteroaryl rings to which it is possible to fuse a benzene ring.

Exemplifying the invention are:

(a) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-hydroxy-2-propyl)thiophene,

(b) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene,

(c) 3-(4-(Aminosulfonyl)phenyl)-2-(4-fluorophenyl)-5-(2-propyl)thiophene,
(d) 3-(4-(Aminosulfonyl)phenyl)-2-cyclohexylthiophene,
(e) 5-(4-Carboxyphenyl)-4-(4-(methylsulfonyl)phenyl)thiophene-2-carboxylic acid,

(f) 4-(4-Fluorophenyl)-2-methyl-5-(4-(methylsulfonyl)phenyl)thiazole,
(g) 2-(4-Fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one
(h) 4-(4-(Methylsulfonyl)phenyl)-5-(4-fluorophenyl)-isothiazole,
(i) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(j) 3-(4-Fluorophenyl)-4-(4-(aminosulfonyl)phenyl)-2-(*5H*)-furanone,
(k) 3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)furan,
(l) 5,5-Dimethyl-3-(4-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(m) 2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)thiophene, and
(n) 3-(4-(Trifluoroacetylaminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene,
(o) 3-(3-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(p) 5,5-Dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(q) 5,5-Dimethyl-3-(3-chlorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(r) 3-(3,4-Difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(s) 3-(3,4-Dichlorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(t) 5,5-Dimethyl-3-(3,4-difluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(u) 5,5-Dimethyl-3-(3,4-dichlorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone,

(v) 5,5-Dimethyl-3-(4-chlorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(w) 3-(2-Naphyhyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(x) 5,5-Dimethyl-3-(2-naphyhyl)-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone,
(y) 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising: administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

For purposes of this specification a preferred compound is said to selectively inhibit COX-2 in preference to COX-1 if the ratio of the

IC50 concentration for COX-1 inhibition to COX-2 inhibition is 100 or greater.

The pharmaceutical compositions used in the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N_-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

For the treatment of any of these cyclooxygenase mediated diseases, compounds of formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethyl-cellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene

oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable

dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of

an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

EXAMPLE

Using PCR analysis of mRNA extracted from the post-mortem hippocampus of 7 AD patients and 6 age-matched control patients (with no history of neurological or neuropsychiatric diseases, we found COX-II mRNA in 6 AD patients. Four of the control patients showed no COX-II mRNA. In situ hybridization histochemistry also showed COX-II mRNA in the hippocampus of 4 AD patients but not in 5 control patients. Western blot analysis of temporal lobe cortex showed COX-II protein in 3AD patients but not in 3 control patients.

These results show that COX-II is induced in the medial temporal lobe of AD patients, a brain region most severely affected during alzheimers disease process. The results indicate that the inflammatory condition associated with AD involve COX-II in its aetiology and show that treating AD patients with brain penetrant selective COX-II inhibitors will be effective.

CLAIMS

1. The use of a non-steroid COX-II inhibitor in the manufacture of a medicament for the treatment of a neurodegenerative disease.
2. The use as claimed in Claim 1 wherein the neurodegenerative disease is Alzheimer's Disease.
3. The use as claimed in Claim 1 or 2 wherein the medicament is adapted for oral administration.
4. The use as claimed in any of Claims 1 to 3 wherein the medicament is in the form of a tablet.
5. The use as claimed in any of Claims 1 to 3 wherein the COX-II inhibitor will bind at least 20 times as well to COX-II as to COX-I.

The use as claimed in any of Claims 1 to 3 wherein the COX-II inhibitor will bind at least 100 times as well to COX-II as to COX-I.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02382

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/10 A61K31/165 A61K31/18 A61K31/33
A61K31/365 A61K31/38 A61K31/40 A61K31/41 A61K31/415
A61K31/42 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 13635 (MERCK FROSST CANADA INC.) 23 June 1994 cited in the application see page 14, line 2 - line 3 ---	1-5
X	WO,A,94 20480 (MERCK FROSST CANADA INC.) 15 September 1994 cited in the application see page 9, line 7 - line 8 ---	1-5
X,P	WO,A,94 26731 (MERCK FROSST CANADA INC.) 24 November 1994 see page 8, line 4 - line 7 ---	1-5
X	WO,A,94 26751 (PFIZER INC.) 24 November 1994 cited in the application see the whole document ---	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
19 February 1996	05.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Theuns, H

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02382

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	WO,A,95 18799 (MERCK FROSST CANADA INC.) 13 July 1995 cited in the application see page 12, line 16 - line 19	1-5
A	EP,A,0 056 956 (SCHERING AKTIENGESELLSCHAFT) 4 August 1982 cited in the application see the whole document	1-5
A	WO,A,91 19708 (FUJISAWA PHARMACEUTICAL CO., LTD.) 26 December 1991 cited in the application see the whole document	1-5
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No	PCT/GB 95/02382

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 15932 (G.D.SEARLE & CO.) 21 July 1994 cited in the application see page 7 -----	1-5

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INTERNATIONAL SEARCH REPORT

national application No.

PCT/GB95/02382

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-5
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 5 appears to consist of more than a single claim. The definition of chemical compounds my means of their pharmacological properties makes a complete search virtually impossible.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02382

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